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ATRA+ATO combination in APL – A commentary on "evolving of treatment paradigms and challenges in acute promyelocytic leukaemia: A real-world analysis of 1105 patients over the last three decades" by Teng-Fei et al.

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Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML) characterized by a balanced reciprocal translocation between chromosomes 15 and 17. In recent years, studies have been carried out on APL treatment in the field of molecular targeting and differentiation therapy. Improvements in response rate and long-term outcomes have been reported as a result of combining all-trans-retinoic acid (ATRA) with chemotherapy treatment methods [1]. The addition of arsenic trioxide (ATO) to treatment strategies increased the survival time of patients and provided long-term remission [2]. In addition, a synergistic effect was noted between ATRA and ATO in inducing the catabolism of the *PML::RARA* fusion protein [2]. The combined use of ATRA and ATO in patients with newly diagnosed APL has shown a curative effect in more than 90% of the patients [3].

The Sanz risk classification is mainstay of APL management [4]. It has also been reported that additional genetic mutations exemplified by *FLT3-ITD* or *TKD* and *NRAS* are associated with prognosis and have a role in predicting relapse and survival [5].

Early death (ED) has been identified as the biggest obstacle to curing APL patients. Studies have shown that while the rate of ED is 5–10% in the use of ATRA only [6–9], it varies between 17.3–29% in the use of ATRA plus chemotherapy [6,7]. The emergence and development of new treatment modalities indicate that clinical trials with inclusion and exclusion criteria are needed. Albeit there are some studies that pored over the real-life efficacy of ATRA+ATO treatment paradigm in population-based settings rather than small, highly selected patient subgroups revealed results that are concordant with the previous results from clinical trials, we still do not have sufficient evidence to truly validate the ATRA+ATO treatment paradigm in a population based cohort [10,11]. Thus, we lack strong evidence for true efficacy and safety of a treatment paradigm and to facilitate more rational therapeutic decisions.

APL treatment has undergone a significant paradigm shift, especially in the last 10 years. Although APL is generally accepted as a treatable disease, ED and relapse have not been adequately evaluated. Moreover, unlike clinical trials based on highly selected APL patients, population-based information reflecting realistic models of the disease is limited, particularly in the era of ATRA+ATO-based stratified therapy.

Teng-Fei et al. [12] retrospectively examined the treatment modalities applied to 1105 patients with APL, and a real evaluation was made by taking the data of the last 30 years from the Shanghai Institute of Hematology (SIH) database. By systematically comparing three calendar periods classified by different treatment modalities, the overall trend of treatment development and its real benefits are explained from a real-world perspective. In addition, was aimed to evaluate the recovery

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of premature deaths due to the treatment modalities applied in the study, consider the prognostic values of additional genetic mutations and present the results related to the risk assessment of APL patients, which can provide a better framework for the future. The study indicated that with the improvement of treatment, the incidence of premature death in APL patients decreased over time. During the period of ATRA plus chemotherapy, the rate of ED was reported to be 20.2% (n = 99) and ranged from 14.6% to 29%, consistent with the data reported in most population-based studies in the same phase [6–9]. It is observed that the rate of ED decreases to 7% in other treatment periods. Intracranial hemorrhage, differentiation syndrome (DS), and infections have been noted among the most common causes of ED. In the study was stated that there was a significant decrease in the last two periods in premature deaths exceeding seven days. It has been noted that the administration of ATRA greatly reduces deaths within seven days, mainly due to intracranial hemorrhage, and experiences with increased ATO, steroids and reduced chemotherapy may help reduce the risk of second-stage DS and ED caused by infections. A decrease in premature mortality and a lower rate of relapse have been reported due to the introduction of ATO. The dose of cytotoxic chemotherapy appears to decrease over time as a result of the widespread adoption of ATRA and ATO in non-high-risk patients [12]. It has shown that the development of treatment paradigms in APL not only prolongs survival, but also saves patients from the toxicity of intensive chemotherapy.

Advanced age and high white blood cell (WBC) counts have proven to be independent adverse factors of overall survival (OS) by combining the ATRA+ATO-based period. In addition, a revised risk scoring model was created for the estimation of OS. It has been stated that a high WBC counts and the presence of *NRAS* mutations increase the tendency to relapse [12]. Accordingly, a revised predictive model for DFS has been developed that can clearly distinguish patients at higher risk of disease recurrence. It has been stated that the development of targeted agents in the chemotherapy process can prevent premature deaths and have positive effects on the treatment of APL patients [12]. It shows that both clinical parameters and molecular markers provide a prognostic value during the ATRA+ATO period and incorporating these indicators into the risk stratification system allows for more accurate estimation of relapse and survival, as well as rapid management of ED risk.

There is compelling evidence that the ATRA+ATO-based combination strategy can protect a group of patients from ED, improve the likelihood of OS and disease-free survival (DFS), and simultaneously reduce the toxicity of chemotherapy. Age, high WBC counts, and NRAS mutations are effective in risk classification and may contribute to disease management. It is thought that the evaluation and classification of patients according to different prognostic markers in determining the treatment strategies of APL will contribute to reducing ED rates and increasing survival rates.

In addition, as we all know, every success comes with a price, and developments in all these treatment modalities may create a financial burden. Most studies which scrutinized cost-effectivity of ATRA+ATO treatment showed this combination, in addition to inducing favorable outcomes in terms of OS and DFS, is also more cost-effective than other conventional therapies such as ATRO+CT strategies for patients newly diagnosed with APL [13,14].

To conclude, as clearly shown by Teng-Fei and colleagues [12], in the real-world setting, ATRA+ATO combination can be beneficial in preventing ED and resulting in superior clinical outcomes. Together with these benefits, this combination can also be more cost-effective when compared to conventional treatment modalities. Prospective studies are still needed to evaluate the treatment strategies of APL in large samples and different prognostic markers.

CRediT authorship contribution statement

Damla Ortaboz: Conceptualization, Methodology, Investigation, Writing – original draft. **Mehmed Semih Çetin:** Writing – original draft. **Burak Cömert:** Writing – original draft. **Ahmet Emre Eşkazan:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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